Does a glass of coke boost the exposure to imatinib in GIST patients after gastrectomy?

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Running head

Boosting imatinib exposure with Coca-cola?

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. In the advanced and metastatic setting, imatinib is the first line treatment.[1] Imatinib has been approved for GIST at a standard dose of 400mg once daily.[2] Due to its oral route of administration, variable absorption can lead to variations in systemic exposure.[3] Changes in stomach pH due to gastric surgery or the use of acid reduction agents may influence absorption of certain oral drugs.[4] However, alterations in stomach pH is not expected to impact imatinib absorption since imatinib dissolves rapidly at a pH range of 1.0–6.8.[5]

Unexpectedly, decreased imatinib exposure has previously been reported in eighteen GIST patients who underwent major gastrectomy.[3] Imatinib trough concentrations (C_{trough}) were significantly reduced compared to patients without gastric surgery (C_{trough} 942±330µg/L versus 1.393±659µg/L).[3] As a result, imatinib trough concentrations where below 1100µg/L in patients with a major gastrectomy. This is important as through concentrations below 1100µg/L are associated with unfavorable treatment response.[3] It emphasizes the potential clinically relevant consequences of prior major gastrectomy for this group of patients.[6]

The exact mechanism that explains reduced imatinib trough concentrations after major gastrectomy is unknown. Yoo et al. suggest that decreased imatinib absorption is caused by an elevated gastric pH which reduces the solubility of imatinib.[3] As seen for other TKIs, exposure can be increased when the gastric pH is artificially lowered by concomitant use of an acidic beverage (e.g. cola).[7]

To investigate whether this proof of concept also applies to imatinib, a small study was performed to explore the effect of concomitant intake of imatinib with Coca-cola on imatinib exposure in GIST patients with major gastrectomy All patients gave informed consent before entering the study. This study was approved by the institutional ethics committee and registered at ClinicalTrials.gov nr:NCT02185937.

In this cross-over study in seven patients with previous gastrectomy, patients used 400mg imatinib once daily taken with a glass of water. After reaching steady-state pharmacokinetics (day 7), a pharmacokinetic (PK) curve of imatinib was assessed at the following timepoints t=0,1,2,3,4,5,6,8 and 10 hours after imatinib intake. Subsequently, imatinib 400mg was concomitantly ingested with 150ml of Coca-Cola classic® (pH 2.4). Again, after reaching steady-state pharmacokinetics (day 14), the PK assessment was repeated. The order in which patients underwent both treatments was randomly assigned. Imatinib plasma concentrations were measured using a validated liquid chromatography tandem mass spectrometry method.[8] The AUC, C_{max}, C_{trough} were calculated using noncompartmental analyses in WinNonlin/Phoenix v6.3 (Pharsight Corporation).

The geometric mean (GM) of the area under the concentration time curve (AUC_{0-24h}) including 95% confidence interval (CI)) was 25769µg/L*h (CI 19553-33960) when imatinib was ingested with Coca-cola; compared to 24881µg/L*h (CI 18318-33795) when imatinib was ingested with water. The GM of C_{trough} and C_{max} ingested with Coca-cola was 789µg/L (CI 594-1049) and 2224µg/L (CI 1854-2670) compared to 662µg/L (CI 487-901) and 2010µg/L (CI 1662-2431) when ingested with water (table 1). The GM-ratio including the 90% CI was 1.04 (CI 0.94-1.14) for $AUC_{0-24h,}$ 1.10 (CI 1.0-0.22) for C_{max} and 1.19 (CI 1.0-1.42) for C_{trough}.[9] The small increase in imatinib exposure due to Coca-cola intake appeared not to be clinically relevant as demonstrated by the GM-ratios. More importantly, the Coca-cola intervention did not elevate trough concentrations above the defined threshold of 1100µg/L. Therefore, it is not expected that ingesting imatinib with Coca-cola in patients with major gastrectomy improves treatment outcome.

In accordance with previous research, mean trough concentrations observed in our study (662±227µg/L) were lower than trough concentrations in patients without gastrectomy (1393±659µg/L).[3] This confirms the earlier observation that patients who underwent major

gastrectomy had a significantly decreased imatinib exposure. Furthermore, we showed that imatinib exposure did not increase to normal levels when exposed to a more acidic environment. Therefore, increase of gastro-intestinal pH after gastrectomy cannot be accounted for the majorly reduced exposure of imatinib. In our study we used 150ml of Coca-cola which is a lower volume than used in previous studies in patients without gastrectomy. Since our patients had no or a significantly reduced stomach volume left the reduced volume of Coca-cola used should be sufficient to induce adequate pH reduction.

The decreased imatinib absorption might be explained by absence of active transporters that are mainly present in the stomach. In a study in mice by Furmanski et al. it was suggested that ABCC4 transporters facilitates dasatinib absorption.[10] These transporters are resected when patient undergo major gastrectomy. Hypothetically, imatinib, like dasatinib absorption is facilitated by these transporters as well. This hypothesis however, needs to be investigated more thoroughly.

Concluding, we confirmed that patients after gastrectomy have a marked reduction in exposure to imatinib which may translate into worse clinical outcome. We could not demonstrate that reintroducing an acid environment led to increased exposure to imatinib. We therefore suggest that the remarkably low exposure of imatinib after major gastrectomy may be due to removal of gastric transporters. Finally, we advise to measure imatinib trough concentrations in all patients with major gastrectomies and personalise imatinib dosing accordingly to prevent ineffective treatment.

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Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [appropriate reference number], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [11, 12].

Conflict of interest

The authors declare no conflict of interest. The study was designed, organized, conducted and funded by academic researchers from two academic hospitals (LUMC and Radboudumc).

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List of Tables and Figures:

Table 1 Pharmacokinetic parameters imatinib

	Water	Cola
AUC_{0-24h}, µg·h/L, GM (GM CV%)	24881 (34.0)	25769 (30.5)
C_{max}, µg/L, GM (GM CV%)	2010.1 (20.8)	2224.5 (19.9)
C_{trough}, mg/L, GM (GM CV%)	662.5 (34.2)	789.4 (31.5)
T_{max}, h, median (range)	2.0 (1-5)	2.0 (1-4)
$T_{1/2}$, h, median (range)	8.9 (5.3-21.2)	11.3 (4.6-12.7)

Abbreviations: AUC_{0-24h}, AUC to 24 hours, Area Under the Concentration time curve; GM, Geometric mean; CV%, percentage of coefficient of variation defined by (standard deviation/mean) x 100; C_{max}, maximum observed plasma concentration; $C_{through}$, plasma concentration at t=24h; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life.

Table 1 Pharmacokinetic parameters imatinib

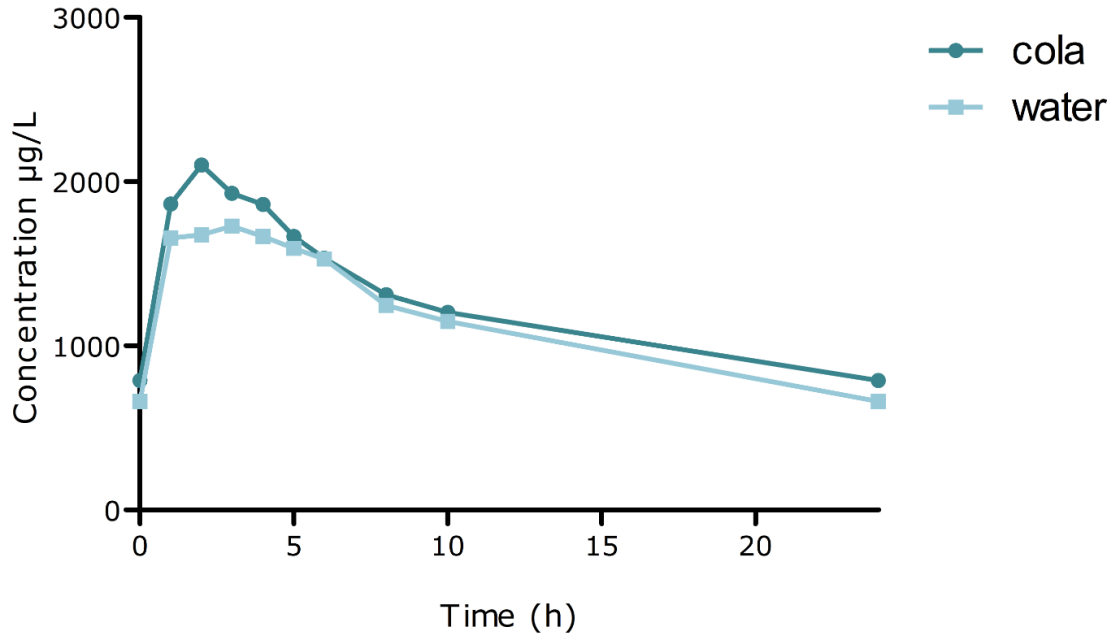

Fig. 1 Patients imatinib exposure

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The study was designed, organized, conducted and funded by academic researchers from two academic hospitals (Radboudumc and LUMC). Clinical investigators gathered study data. All authors had access to the study data. The first and last author wrote the first draft, which was carefully reviewed by all co-authors who approved the final submitted version. The corresponding author had unrestricted access to all the raw study data and had final responsibility for the decision to submit for publication.

Disclaimers

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